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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/018,373
Filing Date: December 06, 2001
Appellant(s): BIGALKE ET AL.

BIGALKE ET AL.
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed October 7, 2008 appealing from the Final Office action mailed June 2, 2008.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

No amendment after final has been filed.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

Keen et al *(Plastic and Reconstructive Surgery, July 1994, 94, No.1, pages 94-99).*

Johnson et al *(U.S. Patent No. 5,512,547 published April 30, 1996).*

Carruthers et al, *Cosmetic Uses of Botulinum Toxin A Exotoxin*. In:Klein AW, ed. *Tissue Augmentation in Clinical Practice: Procedures and Techniques*. New York: Marcel Dekker, 1998:207-236).

Heckman et al *(Arch Dermatol, Vol. 134, October 1998).*

Kessler *(J Neurol (1999) 246:265-274*).

Goschel et al, *(Experimental Neurology, 147, 1997, pages 96-102)*

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

I. Claims 11 and 14-15 are rejected under 35 U.S.C. 103(a) as unpatentable over Keen et al *(Plastic and Reconstructive Surgery, July 1994, 94, No.1, pages 94-99)* in view of Johnson et al *(U.S. Patent No. 5,512,547 published April 30, 1996).*

Keen et al teach a method of treating patients that have hyperkinetic facial lines (wrinkles) with injections of botulinum toxin A (botulinum toxin A complex)(see the Abstract and pages 95-97). Keen et al teach that the injections may be repeated to

achieve the desired effect (page 98). Keen et al teach that botulinum toxin A injections eliminated hyperfunctional facial lines (wrinkles) in healthy aesthetic surgical patients (page 94). Keen et al teach that antibodies to botulinum toxin A have been described in patients receiving much larger dosages of botulinum toxin complex for long periods of time and the antibodies can render the toxin non-effective but do not harm the patient (nonresponders) (page 98). Keen et al teach that the use of botulinum toxin A is a safe and efficacious method of nonsurgically eliminating facial wrinkles in aesthetic surgical patients for a period of 4 to 6 months (page 99).

Keen et al do not teach the claim limitation "wherein the neurotoxins or mixture of neurotoxins is free of the complexing proteins which naturally form complexes with botulinum neurotoxins and wherein the human or animal already exhibits neutralizing antibodies against botulinum neurotoxin complexes".

Johnson et al teach a pharmaceutical composition comprising an essentially pure botulinum toxin A (see the Abstract and column 2). Johnson et al teach that the use of pure neurotoxin instead of the toxin complex, which is used commercially, reduced the amount of toxin required to obtain the necessary number of active U per vial as mandated by the U.S. Food and Drug Administration (column 2). Johnson et al teach that this improvement also reduces the amount of inactive toxin in each vial and thereby lessens the possibility of antibody formation after injection of the preparation into patients (column 2). Johnson et al teach that higher specific activity preparations reduce the probability of patients developing neutralizing antibodies and it would be

obviously desirable to have higher specific activity preparations than those currently available (column 2).

It would be *prima facie* obvious to one of ordinary skill at the time the invention was made to substitute the botulinum toxin A (botulinum toxin A complex) in the method of treating patients with hyperkinetic facial lines (wrinkles) as taught by Keen et al with the pure botulinum toxin A (without complexing proteins) as taught by Johnson et al because Johnson et al teach that purified product reduces the amount of inactive toxin in each vial and thereby lessens the possibility of antibody formation after injection of the preparation into patients. It would be expected absent, evidence to the contrary, that a composition comprising pure botulinum toxin A (without complexing proteins) would be effective in treating patients that are nonresponders (have neutralizing antibodies to botulinum toxin A complex) because Johnson et al teach that higher specific activity preparations reduce the probability of patients developing neutralizing antibodies and it would be obviously desirable to have higher specific activity preparations than those currently available (column 2).

Additionally, *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007), discloses that if a technique has been used to improve one method , and a person of ordinary skill would recognize that it would be used in similar methods in the same way, using the technique is obvious unless its application is beyond that person's skill. *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) also discloses that "The combination of familiar element according to known methods is likely to be obvious when it does no more than yield predictable results". It well known in the art to use

botulinum toxin complex to treat cosmetic conditions such as hyperhidrosis and facial wrinkling. Keen et al recognize that patients receiving much larger dosages of botulinum toxin complex for long periods of time may produce neutralizing antibodies to the botulinum toxin complex. Johnson et al also recognize that there is a need in the art to solve the problem of the development of neutralizing antibodies to the botulinum toxin complex. Johnson et al provide a solution to this problem, by preparing a product that is pure neurotoxin instead of the complex. Thus, it would be obvious to apply a known technique to a known product to be used in a known method that is ready for improvement to yield predictable results.

II. Claims 11-15 are rejected under 35 U.S.C. 103(a) as unpatentable over Carruthers et al, *Cosmetic Uses of Botulinum Toxin A Exotoxin*. In:Klein AW, ed. *Tissue Augmentation in Clinical Practice: Procedures and Techniques*. New York: Marcel Dekker, 1998:207-236) in view of Heckman et al *(Arch Dermatol, Vol 134, October 1998)* and further in view of Johnson et al *(U.S. Patent No. 5,512,547 published April 30, 1996).*

Claims 11-15 are directed to a method of treating a human or animal cosmetic condition treatable with a botulinum toxin neurotoxin (wrinkling or facial wrinkling, claims 14-15 or hyperhidrosis, claim 13) comprising administering to the human or animal, a treatment effective amount of a botulinum neurotoxin from *Clostridium botulinum* of Type A, B, C, D, E, F or G or a mixture of two or more botulinum neurotoxins, wherein the neurotoxins or mixture of neurotoxins is free of the complexing

proteins which naturally form complexes with botulinum neurotoxins and wherein the human or animal already exhibits neutralizing antibodies against botulinum neurotoxin complexes.

Carruthers et al teach a method of treating cosmetic conditions such as glabellar frown lines Crow's feet and horizontal forehead lines, (all forms of wrinkles) by administering botulinum toxin A complex (Botox® and Dysport®) (pages 210 and 214-230, See for example page 215, Figure 1). Carruthers et al teach that incidence of treatment resistance to botulinum toxin A usually varies with the amount of exposure to the toxin (page 212). Carruthers et al teach that in neurologic patients, it is estimated that one-third of all treatment failures may be the result of the development of antibodies (page 214). Carruthers et al teach that patients injected toxin doses greater than 100 units/session, patients receiving booster injections within 30 days of initial botulinum toxin injection and injection of toxin into systemic circulation may develop antibodies against botulinum toxin A complex (page 213).

Carruthers et al teach do not teach the claim limitation "the cosmetic wherein the cosmetic treatment is for hyperhidrosis (excessive sweating, a cosmetic condition).

Heckman et al teach that after 1-year follow-up of patients that received 500 U per axilla of botulinum toxin injection for axillary hyperhidrosis, 3 out of 12 patients showed mitigated recurrence of axillary hyperhidrosis after 3, 4 and 7 months, respectively, which could be overcome by a second injection of botulinum toxin (page 1298).

Carruthers et al and Heckman et al teach do not teach the claim limitation "wherein the neurotoxins or mixture of neurotoxins is free of the complexing proteins which naturally form complexes with botulinum neurotoxins and wherein the human or animal already exhibits neutralizing antibodies against botulinum neurotoxin complexes".

Johnson et al teach a pharmaceutical composition comprising an essentially pure botulinum toxin A (see the Abstract and column 2). Johnson et al teach that the use of pure neurotoxin instead of the toxin complex, which is used commercially, reduced the amount of toxin required to obtain the necessary number of active U per vial as mandated by the U.S. Food and Drug Administration (column 2). Johnson et al teach that this improvement also reduces the amount of inactive toxin in each vial and thereby lessens the possibility of antibody formation after injection of the preparation into patients (column 2). Johnson et al teach that higher specific activity preparations reduce the probability of patients developing neutralizing antibodies and it would be obviously desirable to have higher specific activity preparations than those currently available (column 2).

It would be *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute the botulinum toxin A (botulinum toxin A complex) in the method of treating patients with hyperhidrosis as taught by Carruthers et al and Heckman et al with the pure botulinum toxin A (without complexing proteins) as taught by Johnson et al because Johnson et al teach that purified product reduces the amount of inactive toxin in each vial and thereby lessens the possibility of antibody formation

after injection of the preparation into patients. It would be expected absent, evidence to the contrary, that a composition comprising pure botulinum toxin A (without complexing proteins) would be effective in treating patients that are nonresponders (have neutralizing antibodies to botulinum toxin A complex) because Johnson et al teach that higher specific activity preparations reduce the probability of patients developing neutralizing antibodies and it would be obviously desirable to have higher specific activity preparations than those currently available (column 2).

Additionally, *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007), discloses that if a technique has been used to improve one method , and a person of ordinary skill would recognize that it would be used in similar methods in the same way, using the technique is obvious unless its application is beyond that person's skill. *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) also discloses that "The combination of familiar element according to known methods is likely to be obvious when it does no more than yield predictable results". It well known in the art to use botulinum toxin complex to treat cosmetic conditions such as hyperhidrosis and facial wrinkling. Carruthers et al recognize that patients receiving much larger dosages of botulinum toxin complex for long periods of time may produce neutralizing antibodies to the botulinum toxin complex. Johnson et al also recognize that there is a need in the art to solve the problem of the development of neutralizing antibodies to the botulinum toxin complex. Johnson et al provide a solution to this problem, by preparing a product that is pure neurotoxin instead of the complex. Thus, it would be obvious to apply a

known technique to a known product to be used in a known method that is ready for improvement to yield predictable results.

III. Claims 16-18 are rejected under 35 U.S.C. 103(a) as unpatentable over Kessler *(J Neurol (1999) 246:265-274*) in view of Johnson et al *(U.S. Patent No. 5,512,547 published April 30, 1996).*

Claims 16-18 are directed to a method of treating a human or animal with dystonia or nervous system disorder treatable with a botulinum toxin neurotoxin (dystonia, claim 18) comprising administering to the human or animal, a treatment effective amount of a botulinum neurotoxin from *Clostridium botulinum* of Type A, B, C, D, E, F or G or a mixture of two or more botulinum neurotoxins, wherein the neurotoxins or mixture of neurotoxins is free of the complexing proteins which naturally form complexes with botulinum neurotoxins and wherein the human or animal already exhibits neutralizing antibodies against botulinum neurotoxin complexes.

Kessler et al teach long-term treatment of cervical dystonia (CD) with botulinum toxin A (see the Title and the Abstract). Kessler et al teach that the only risk of botulinum toxin injections is the development of serum antibodies against the toxin (see the Abstract).Kessler et al teach that 2% of patients of the study developed neutralizing antibodies (see Abstract). Kessler et al teach that among the 162 patient who discontinued therapy, 17 reported having lost their initially beneficial effect (page 271). Kessler et al teach that at least one of the tests performed detected neutralizing serum antibodies in 9 of the 17 patients who clinically fulfilled the criteria for secondary

nonresponse (page 271). Kessler et al teach that secondary nonresponse is one of the major problems in long-term treatment of CD with botulinum toxin A because it entails discontinuing, depriving the patient of the most successful therapy available (page 272). Kessler et al teach that this study confirms that patients at risk of developing neutralizing antibodies are those with high doses administered at relatively short intervals which is in good agreement with previous studies on the issue (page 273).

Kessler et al do not teach the claim limitation "wherein the neurotoxins or mixture of neurotoxins is free of the complexing proteins which naturally form complexes with botulinum neurotoxins and wherein the human or animal already exhibits neutralizing antibodies against botulinum neurotoxin complexes".

Johnson et al teach a pharmaceutical composition comprising an essentially pure botulinum toxin A (see the Abstract and column 2). Johnson et al teach that the use of pure neurotoxin instead of the toxin complex, which is used commercially, reduced the amount of toxin required to obtain the necessary number of active U per vial as mandated by the U.S. Food and Drug Administration (column 2). Johnson et al teach that this improvement also reduces the amount of inactive toxin in each vial and thereby lessens the possibility of antibody formation after injection of the preparation into patients (column 2). Johnson et al teach that higher specific activity preparations reduce the probability of patients developing neutralizing antibodies and it would be obviously desirable to have higher specific activity preparations than those currently available (column 2).

It would be *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute the botulinum toxin A (supplied by Dysport, Speywood, U.K. botulinum toxin A complex) in the method of treating patients with cervical dystonia as taught by Kessler with the pure botulinum toxin A (without complexing proteins) as taught by Johnson et al because Johnson et al teach that purified product reduces the amount of inactive toxin in each vial and thereby lessens the possibility of antibody formation after injection of the preparation into patients. It would be expected absent, evidence to the contrary, that a composition comprising pure botulinum toxin A (without complexing proteins) would be effective in treating patients that are secondary nonresponders (have neutralizing antibodies to botulinum toxin A complex) because Johnson et al teach that higher specific activity preparations reduce the probability of patients developing neutralizing antibodies and it would be obviously desirable to have higher specific activity preparations than those currently available (column 2).

Additionally, *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007), discloses that if a technique has been used to improve one method , and a person of ordinary skill would recognize that it would be used in similar methods in the same way, using the technique is obvious unless its application is beyond that person's skill. *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) also discloses that "The combination of familiar element according to known methods is likely to be obvious when it does no more than yield predictable results". It well known in the art to use botulinum toxin complex to treat cosmetic conditions such as hyperhidrosis and facial

wrinkling. Kessler et al recognize that patients receiving much larger dosages of botulinum toxin complex for long periods of time may produce neutralizing antibodies to the botulinum toxin complex. Johnson et al also recognize that there is a need in the art to solve the problem of the development of neutralizing antibodies to the botulinum toxin complex. Johnson et al provide a solution to this problem, by preparing a product that is pure neurotoxin instead of the complex. Thus, it would be obvious to apply a known technique to a known product to be used in a known method that is ready for improvement to yield predictable results.

IV. Claims 16-18 are rejected under 35 U.S.C. 103(a) as unpatentable over Goschel et al, *(Experimental Neurology, 147, 1997, pages 96-102)* in view of Johnson et al *(U.S. Patent No. 5,512,547 published April 30, 1996).*

Claims 16-18 are directed to a method of treating a human or animal a dystonia or a nervous system disorder treatable with a botulinum toxin neurotoxin (dystonia, claim 18) comprising administering to the human or animal, a treatment effective amount of a botulinum neurotoxin from *Clostridium botulinum* of Type A, B, C, D, E, F or G or a mixture of two or more botulinum neurotoxins, wherein the neurotoxins or mixture of neurotoxins is free of the complexing proteins which naturally form complexes with botulinum neurotoxins and wherein the human or animal already exhibits neutralizing antibodies against botulinum neurotoxin complexes.

Goschel et al teach a method of using botulinum toxin to treat patients having torticollis spasmodicus, facial dystonias, torsion dystonia and spasticity patients (pages

98-99 and Table 3, page 101). Goschel et al also teach patients that have developed neutralizing antibodies against botulinum toxin A complex (pages 98-99 and Table 3, page 101). Goschel et al teach that neutralizing antibodies were the cause of therapeutic failure (page 101). Goschel et al teach that based on theses studies, second generation botulinum neurotoxin preparations should be devoid of toxoid and should be purified from concomitant proteins, this will reduce the load of foreign substances that might lead to untoward reactions (page 102).

Goschel et al do not teach the claim limitation "wherein the neurotoxins or mixture of neurotoxins is free of the complexing proteins which naturally form complexes with botulinum neurotoxins and wherein the human or animal already exhibits neutralizing antibodies against botulinum neurotoxin complexes".

Johnson et al teach a pharmaceutical composition comprising an essentially pure botulinum toxin A (see the Abstract and column 2). Johnson et al teach that the use of pure neurotoxin instead of the toxin complex, which is used commercially, reduced the amount of toxin required to obtain the necessary number of active U per vial as mandated by the U.S. Food and Drug Administration (column 2). Johnson et al teach that this improvement also reduces the amount of inactive toxin in each vial and thereby lessens the possibility of antibody formation after injection of the preparation into patients (column 2). Johnson et al teach that higher specific activity preparations reduce the probability of patients developing neutralizing antibodies and it would be obviously desirable to have higher specific activity preparations than those currently available (column 2).

It would be *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute the botulinum toxin A (botulinum toxin A complex) in the method of treating patients with a dystonia or a nervous system disorder treatable with botulinum neurotoxin as taught by Goschel et al with the pure botulinum toxin A (without complexing proteins) as taught by Johnson et al because Johnson et al teach that purified product reduces the amount of inactive toxin in each vial and thereby lessens the possibility of antibody formation after injection of the preparation into patients. It would be expected absent, evidence to the contrary, that a composition comprising pure botulinum toxin A (without complexing proteins) would be effective in treating patients that are nonresponders (have neutralizing antibodies to botulinum toxin A complex) because Johnson et al teach that higher specific activity preparations reduce the probability of patients developing neutralizing antibodies and it would be obviously desirable to have higher specific activity preparations than those currently available (column 2).

Additionally, *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007), discloses that if a technique has been used to improve one method, and a person of ordinary skill would recognize that it would be used in similar methods in the same way, using the technique is obvious unless its application is beyond that person's skill. *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) also discloses that "The combination of familiar element according to known methods is likely to be obvious when it does no more than yield predictable results". It well known in the art to use botulinum toxin complex to treat cosmetic conditions such as hyperhidrosis and facial

wrinkling. Goschel et al recognize that patients receiving much larger dosages of botulinum toxin complex for long periods of time may produce neutralizing antibodies to the botulinum toxin complex. Goschel et al even suggest that second generation botulinum neurotoxin preparations should be devoid of toxoid and should be purified from concomitant proteins, this will reduce the load of foreign substances that might lead to untoward reactions. Johnson et al also recognize that there is a need in the art to solve the problem of the development of neutralizing antibodies to the botulinum toxin complex. Johnson et al provide a solution to this problem, by preparing a product that is pure neurotoxin instead of the complex. Thus, it would be obvious to apply a known technique to a known product to be used in a known method that is ready for improvement to yield predictable results.

(10) Response to Argument

I. Appellants Specific Arguments Restated

A) Appellant urges that the Examiner has not established a proper case of prima facie obviousness. Appellant urges that the Examiner has not established that all limitations are taught or suggested by the prior art. Appellant urges that Keen et al and Johnson et al do not teach or suggest the instant claim limitation to administration of a *Clostridium botulinum* neurotoxin which is free of complexing proteins in subjects already exhibiting neutralizing antibodies. Appellant urges that Johnson et al state that "This improvement also reduces the amount of inactive toxin (toxoid) in each vial and thereby lessens the possibility of antibody formation after injection of the

preparation into patients". Appellant urges that the Examiner acknowledges that Johnson et al teach that " higher specific activity preparations reduce the probability of patients developing neutralizing antibodies". Appellant urges that Johnson et al teach that one way to reduce the number of patients developing neutralizing antibodies would be to develop a more shelf-stable product with a higher specific activity following lyophilization. Appellant urges that Johnson et al teach that a formulation would result in a product that is not antigenic as the currently available product and lesser quantities would be required for treatment". Appellant teaches that Johnson et al state " The toxin is recognized by patient's immune systems as foreign and stimulates antibody production. This renders treatment of the various hyperactive muscle disorders with botulinum toxin ineffective." Appellant teaches that Johnson et al nor Keen et al teach the critical claim limitation "wherein the human or animal already exhibits neutralizing antibodies against botulinum neurotoxin complexes". Appellant urges that the Examiner had not established a proper rejection for prima facie obviousness by identifying a motivation to combine the teaching of the prior art references.

B) Appellant urges that the mere fact that references can be combined or modified does not render the resulting combination obvious unless the results would have been predictable to one skilled in the art.

Appellant urges that the Examiner has misapplied and fails to substantiate a finding of obviousness under KSR Interantional Co. v. Teleflex inc. Appellant urges that the improvement method of the cited art according to the Examiner's method has

already been demonstrated on the record to be a method which not comparable to the instant method of treating subjects who already exhibits neutralizing antibodies to botulinum toxin complexes. Appellant urges that according to MPEP 2143 interpretation of KSR to reject the claims based on the "obvious to try" exemplary rationale to support a finding of obviousness, the Examiner must articulate a finding that there had been a finite number of identified predictable protential solutions to the recognized need or problem and that one of ordinary skill in the art could have pursued the known potential solutions with a reasonable expectation of success.

Examiner's Response to Applicant's Arguments

I. A) In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

In this case, Keen et al teach the administration of botulinum toxin to patients for cosmetic conditions treatable by botulinum toxin (e.g. hyperfunctional facial lines (wrinkles)). Keen et al teach that patients that receive large dosages of botulinum toxin complex over long periods of time can render the toxin non-effective (e.g. these patients are non-responders). Keen et al do teach a composition of botulinum toxin that

is free from complexing proteins. However, Johnson et al teach compositions of pure botulinum toxin that are free from non-complexing proteins. Johnson et al teach the compositions of the invention reduces the amount of inactive toxin in each vial and thereby lessens the possibility of antibody formation after injection of the composition into patients. One of ordinary skill in the art would reasonably conclude that the compositions taught by Johnson et al comprise botulinum toxin formulations that lessen or reduce neutralizing antibodies because it contains essentially pure botulinum toxin. Johnson et al recognize patients that have developed neutralizing antibodies to the complex are a growing concern in the art, thus this is the very bases for the development of compositions comprising" essentially pure botulinum toxin". Therefore, it would be obvious to administer these compositions to patients that have developed neutralizing antibodies to the botulinum toxin complex. Additionally, *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007), discloses that if a technique has been used to improve one method, and a person of ordinary skill would recognize that it would be used in similar methods in the same way, using the technique is obvious unless its application is beyond that person's skill. *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) also discloses that "The combination of familiar element according to known methods is likely to be obvious when it does no more than yield predictable results". It is well known in the art to use botulinum toxin complex to treat cosmetic conditions such as facial wrinkling. See Keen et al. It is also well known in the art that patients given high dosages of botulinum toxin complex over long periods of time develop neutralizing antibodies. See both Keen et al and Johnson et al. Johnson

et al also recognized that there is a need in the art to solve the problem of the development of neutralizing antibodies to the botulinum toxin complex. Johnson et al provided a solution to this problem, by preparing a product that is a pure neurotoxin instead of the complex. Thus, it would be obvious to administer an essential pure composition of botulinum toxin (e.g. free of complexing proteins) to patients that have neutralizing antibodies because the composition of essentially pure botulinum toxin was developed to lessen or reduce the amount of neutralizing antibodies produced in patients after administration of the composition. It should also be noted that "obvious to try" is proper when there is a finding of a recognized problem or need in the art including a design need or market pressure to solve a problem, a finding that there has been a finite number of identified predictable potential solutions and a finding that one of ordinary skill in the art could have pursed the known potential options with a reasonable expectation of success. See KSR International Co. v. Teleflex Inc., 220 U.S. -, 82 USPQ2d 1385 (2007).

In the instant case, there is a need in the art to find a solution to the problem of development of neutralizing antibodies in patients administered botulinum toxin complex over long periods of time. Since these patients exist there is the problem of treating these patients after botulinum toxin complex injection has failed. Johnson et al developed compositions of essentially pure botulinum toxin to overcome these problems recognized in the prior art. This provides further support as to why one of skill in the art would administer a composition of essentially pure botulinum toxin to patients that have developed neutralizing antibodies to botulinum toxin complex.

In response to Applicant's comments regarding, Johnson et al, as stated above, it is the Examiner's position that Applicant has mischaracterized this passage in Johnson et al. It should be noted that the passage in question is in the Background Section of Johnson et al. In this passage, Johnson et al explain problems in the art associated with patients that have developed neutralizing antibodies to the botulinum toxin complex. Johnson et al recognized the problems associated with patients that have developed neutralizing antibodies to the complex and thus, developed compositions of "essentially pure botulinum toxin" which reduces the amount of inactive toxin in each vial and thereby lessens the possibility of antibody formation after injection of the composition into patients. Therefore, Johnson et al do not teach away from the claimed invention, but in fact, solve the problem associated with patients that have developed neutralizing antibodies to botulinum toxin complex. Therefore, administration of the pure botulinum toxin as taught by Johnson et al to patients that have developed neutralizing antibodies as recognized by the art would be effective.

To address Appellant's argument regarding, Johnson et al statement regarding treatment of the various hyperactive muscle disorders with botulinum toxin ineffective, it should be noted that Johnson et al teach that one of the major drawbacks to the use of botulinum toxin is development of antibodies or other types of immunity by patients (column 1). Johnson et al states:

> "The toxin is recognized by the patient's immune systems as foreign and stimulates antibody production. *Johnson et al teach that this renders treatment of various hyperactive muscle disorders with botulinum toxin ineffective.* One way to reduce the number of patients developing neutralizing antibodies would be to develop neutralizing antibodies would be to develop a more shelf-stable product with a higher specific activity following lyophilization. Such a

> formulation would result in a product that is not antigenic as the currently available product and lesser quantities of toxin would be required for treatment" (column 1).

The context of this passage discloses that the art recognizes that there is a population of patients that have developed neutralizing antibodies. This passage also suggest that a way to reduce the development of neutralizing antibodies is to produce a product with a higher specific activity. Johnson et al has developed such a product, e.g. purified botulinum toxin (without complexing proteins). The statement regarding "Johnson et al teach that this renders treatment of various hyperactive muscle disorders with botulinum toxin ineffective" refers to the *previous products* of the art, e.g. botulinum toxin complex (containing neutralizing antibodies)(e.g. BOTOX®) which includes complexing proteins. This statement does not refer to the ineffectiveness of the products taught by Johnson et al.

To address Appellant's arguments regarding KSR, it should be remembered that MPEP section 2145 states:

> ">A suggestion or motivation to combine references is an appropriate method for determining obviousness, however it is just one of a number of valid rationales for doing so. The Court in KSR identified several exemplary rationales to support a conclusion of obviousness which are consistent with the proper "functional approach" to the determination of obviousness as laid down in Graham. KSR, 550 U.S. at ___, 82USPQ2d at 1395-97. See MPEP § 2141 and § 2143.<

The claimed invention falls within at least two areas of exemplary rationales available under KSR, 550 U.S. at ___, 82USPQ2d at 1395-97. The rationales are as follows:

A. Combining Prior Art Elements According to Known Methods To Yield Predictable Results

The rationale to support a conclusion that the claim would have been obvious is that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination yielded nothing more than predictable results to one of ordinary skill in the art. KSR, 550 U.S. at ___, 82 USPQ2d at 1395; Sakraida v. AG Pro, Inc., 425 U.S. 273, 282, 189 USPQ 449, 453 (1976); Anderson 's-Black Rock, Inc. v. Pavement Salvage Co., 396 U.S. 57, 62-63, 163 USPQ 673, 675 (1969); Great Atlantic & P. Tea Co. v. Supermarket Equipment Corp., 340 U.S. 147, 152, 87 USPQ 303, 306 (1950). "[I]t can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." KSR, 550 U.S. at ___, 82 USPQ2d at 1396. If any of these findings cannot be made, then this rationale cannot be used to support a conclusion that the claim would have been obvious to one of ordinary skill in the art.

In the instant case, compositions comprising botulinum toxin without complexing proteins are known in the art. See Johnson et al. It is also known in the art that patients develop neutralizing antibodies. See Keen et al. Thus, it would be obvious to use a known product in a known method that would do more than yield predictable results. Therefore, absent any convincing evidence to the contrary, the claimed invention is prima facie obvious in view of the combined teachings of Keen et al and Johnson et al.

B. Obvious To Try Rationale

An applicant may argue the examiner is applying an improper “obvious to try” rationale in support of an obviousness rejection.

>An “obvious to try” rationale may support a conclusion that a claim would have been obvious where one skilled in the art is choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success. “ [A] person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely that product [was] not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103.” KSR International Co. v. Teleflex Inc., 550 U.S. ___, ___, 82 USPQ2d 1385, 1397 (2007).<

“The admonition that obvious to try’ is not the standard under § 103 has been directed mainly at two kinds of error. In some cases, what would have been obvious to try’ would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful.... In others, what was obvious to try’ was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.” In re O ’Farrell, 853 F.2d 894, 903, 7 USPQ2d 1673,

1681 (Fed. Cir. 1988) (citations omitted) (The court held the claimed method would have been obvious over the prior art relied upon because one reference contained a detailed enabling methodology, a suggestion to modify the prior art to produce the claimed invention, and evidence suggesting the modification would be successful.).

In the instant case, it would be obvious to administer pure botulinum toxin to patients that have neutralizing antibodies because Johnson et al teach that the compositions of the invention reduces the chances of patients developing neutralizing antibodies.

There is nothing on the record to show that the combination of prior art reference does not teach or suggest the claimed invention.

In view of all of the above, this rejection is maintained.

II. Appellants Specific Arguments Restated

A) Appellant urges that the Examiner has not established a proper case of prima facie obviousness. Appellant urges that the Examiner has not established that all limitations are taught or suggested by the prior art. Appellant urges that Carruthers et al, Heckman et al and Johnson et al do not teach or suggest the instant claim limitation to administration of a *Clostridium botulinum* neurotoxin which is free of complexing proteins in subjects already exhibiting neutralizing antibodies. Appellant urges that Johnson et al state that "This improvement also reduces the amount of inactive toxin (toxoid) in each vial and thereby lessens the possibility of antibody formation after injection of the preparation into patients". Appellant urges that the Examiner

acknowledges that Johnson et al teach that " higher specific activity preparations reduce the probability of patients developing neutralizing antibodies". Appellant urges that Johnson et al teach that one way to reduce the number of patients developing neutralizing antibodies would be to develop a more shelf-stable product with a higher specific activity following lyophilization. Appellant urges that Johnson et al teach that a formulation would result in a product that is not antigenic as the currently available product and lesser quantities would be required for treatment". Appellant teaches that Johnson et al state " The toxin is recognized by patient's immune systems as foreign and stimulates antibody production. This renders treatment of the various hyperactive muscle disorders with botulinum toxin ineffective." Appellant teaches that Johnson et al nor Heckman et al or Carruthers et al teach the critical claim limitation "wherein the human or animal already exhibits neutralizing antibodies against botulinum neurotoxin complexes". Appellant urges that the Examiner had not established a proper rejection for prima facie obviousness by identifying a motivation to combine the teaching of the prior art references.

B) Appellant urges that the mere fact that references can be combined or modified does not render the resulting combination obvious unless the results would have been predictable to one skilled in the art.

Appellant urges that the Examiner has misapplied and fails to substantiate a finding of obviousness under KSR International Co. v. Teleflex inc. Appellant urges that the improvement method of the cited art according to the Examiner's method has

already been demonstrated on the record to be a method which not comparable to the instant method of treating subjects who already exhibits neutralizing antibodies to botulinum toxin complexes. Appellant urges that according to MPEP 2143 interpretation of KSR to reject the claims based on the "obvious to try" exemplary rationale to support a finding of obviousness, the Examiner must articulate a finding that there had been a finite number of identified predictable potential solutions to the recognized need or problem and that one of ordinary skill in the art could have pursued the known potential solutions with a reasonable expectation of success.

II. *Examiner's Response to Applicant's Arguments*

A) In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

In this case, Carruthers et al teach a method of treating cosmetic conditions such as glabellar frown lines Crow's feet and horizontal forehead lines, (all forms of wrinkles) by administering botulinum toxin A complex (Botox® and Dysport). Carruthers et al teach that in neurologic patients, it is estimated that one-third of all treatment failures may be the result of the development of antibodies (page 214). Carruthers et

al teach that patients injected toxin doses greater than 100 units/session, patients receiving booster injections within 30 days of initial botulinum toxin injection and injection of toxin into systemic circulation may develop antibodies against botulinum toxin A complex (page 213). Carruthers et al teach do not teach the claim limitation "the cosmetic wherein the cosmetic treatment is for hyperhidrosis (excessive sweating, a cosmetic condition). Heckman et al teach that after 1-year follow-up of patients that received 500 U per axilla of botulinum toxin injection for axillary hyperhidrosis, 3 out of 12 patients showed mitigated recurrence of axillary hyperhidrosis after 3, 4 and 7 months, respectively, which could be overcome by a second injection of botulinum toxin (page 1298). Carruthers et al and Heckman et al teach do not teach the claim limitation "wherein the neurotoxins or mixture of neurotoxins is free of the complexing proteins which naturally form complexes with botulinum neurotoxins and wherein the human or animal already exhibits neutralizing antibodies against botulinum neurotoxin complexes". However, Johnson et al teach compositions of pure botulinum toxin that are free from non-complexing proteins. Johnson et al teach the compositions of the invention reduces the amount of inactive toxin in each vial and thereby lessens the possibility of antibody formation after injection of the composition into patients. One of ordinary skill in the art would reasonably conclude that the compositions taught by Johnson et al comprise botulinum toxin formulations that lessen or reduce neutralizing antibodies because it contains essentially pure botulinum toxin. Johnson et al recognize patients that have developed neutralizing antibodies to the complex are a growing concern in the art, thus this is the very bases for the development of

compositions comprising" essentially pure botulinum toxin". Therefore, it would be obvious to administer these compositions to patients that have developed neutralizing antibodies to the botulinum toxin complex. Additionally, *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007), discloses that if a technique has been used to improve one method, and a person of ordinary skill would recognize that it would be used in similar methods in the same way, using the technique is obvious unless its application is beyond that person's skill. *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) also discloses that "The combination of familiar element according to known methods is likely to be obvious when it does no more than yield predictable results". It is well known in the art to use botulinum toxin complex to treat cosmetic conditions such as facial wrinkling and hyperhidrosis. See Carruthers et al and Heckman et al, respectively. It is also well known in the art that patients given high dosages of botulinum toxin complex over long periods of time develop neutralizing antibodies. See both Carruthers et al and Johnson et al. Johnson et al also recognized that there is a need in the art to solve the problem of the development of neutralizing antibodies to the botulinum toxin complex. Johnson et al provided a solution to this problem, by preparing a product that is a pure neurotoxin instead of the complex. Thus, it would be obvious to administer an essential pure composition of botulinum toxin (e.g. free of complexing proteins) to patients that have neutralizing antibodies because the composition of essentially pure botulinum toxin was developed to lessen or reduce the amount of neutralizing antibodies produced in patients after administration of the composition. It should also be noted that "obvious to try" is proper when there is a

finding of a recognized problem or need in the art including a design need or market pressure to solve a problem, a finding that there has been a finite number of identified predictable potential solutions and a finding that one of ordinary skill in the art could have pursed the known potential options with a reasonable expectation of success. See KSR International Co. v. Teleflex Inc., 220 U.S. -, 82 USPQ2d 1385 (2007).

In the instant case, there is a need in the art to find a solution to the problem of development of neutralizing antibodies in patients administered botulinum toxin complex over long periods of time. Since these patients exist there is the problem of treating these patients after botulinum toxin complex injection has failed. Johnson et al developed compositions of essentially pure botulinum toxin to overcome these problems recognized in the prior art. This provides further support as to why one of skill in the art would administer a composition of essentially pure botulinum toxin to patients that have developed neutralizing antibodies to botulinum toxin complex.

In response to Applicant's comments regarding, Johnson et al, as stated above, it is the Examiner's position that Applicant has mischaracterized this passage in Johnson et al. It should be noted that the passage in question is in the Background Section of Johnson et al. In this passage, Johnson et al explain problems in the art associated with patients that have developed neutralizing antibodies to the botulinum toxin complex. Johnson et al recognized the problems associated with patients that have developed neutralizing antibodies to the complex and thus, developed compositions of "essentially pure botulinum toxin" which reduces the amount of inactive toxin in each vial and thereby lessens the possibility of antibody formation after

injection of the composition into patients. Therefore, Johnson et al do not teach away from the claimed invention, but in fact, solve the problem associated with patients that have developed neutralizing antibodies to botulinum toxin complex. Therefore, administration of the pure botulinum toxin as taught by Johnson et al to patients that have developed neutralizing antibodies as recognized by the art would be effective.

To address Appellant's argument regarding, Johnson et al statement regarding treatment of the various hyperactive muscle disorders with botulinum toxin ineffective, it should be noted that Johnson et al teach that one of the major drawbacks to the use of botulinum toxin is development of antibodies or other types of immunity by patients (column 1). Johnson et al states:

> "The toxin is recognized by the patient's immune systems as foreign and stimulates antibody production. *Johnson et al teach that this renders treatment of various hyperactive muscle disorders with botulinum toxin ineffective.* One way to reduce the number of patients developing neutralizing antibodies would be to develop neutralizing antibodies would be to develop a more shelf-stable product with a higher specific activity following lyophilization. Such a formulation would result in a product that is not antigenic as the currently available product and lesser quantities of toxin would be required for treatment" (column 1).

The context of this passage discloses that the art recognizes that there is a population of patients that have developed neutralizing antibodies. This passage also suggest that a way to reduce the development of neutralizing antibodies is to produce a product with a higher specific activity. Johnson et al has developed such a product, e.g. purified botulinum toxin (without complexing proteins). The statement regarding "Johnson et al teach that this renders treatment of various hyperactive muscle disorders with botulinum toxin ineffective" refers to the *previous products* of the art, e.g. botulinum

toxin complex (containing neutralizing antibodies)(e.g. BOTOX®) which includes complexing proteins. This statement does not refer to the ineffectiveness of the products taught by Johnson et al.

To address Appellant's arguments regarding KSR, it should be remembered that MPEP section 2145 states:

> ">A suggestion or motivation to combine references is an appropriate method for determining obviousness, however it is just one of a number of valid rationales for doing so. The Court in KSR identified several exemplary rationales to support a conclusion of obviousness which are consistent with the proper "functional approach" to the determination of obviousness as laid down in Graham. KSR, 550 U.S. at ___, 82USPQ2d at 1395-97. See MPEP § 2141 and § 2143.<

The claimed invention falls within at least two areas of exemplary rationales available under KSR, 550 U.S. at ___, 82USPQ2d at 1395-97. The rationales are as follows:

A. Combining Prior Art Elements According to Known Methods To Yield Predictable Results

The rationale to support a conclusion that the claim would have been obvious is that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination yielded nothing more than predictable results to one of ordinary skill in the art. KSR, 550 U.S. at ___, 82 USPQ2d at 1395; Sakraida v. AG Pro, Inc., 425 U.S. 273, 282, 189 USPQ 449, 453 (1976); Anderson 's-Black Rock, Inc. v. Pavement Salvage Co., 396 U.S. 57, 62-63, 163 USPQ 673, 675 (1969);

Great Atlantic & P. Tea Co. v. Supermarket Equipment Corp., 340 U.S. 147, 152, 87 USPQ 303, 306 (1950). "[I]t can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." KSR, 550 U.S. at ___, 82 USPQ2d at 1396. If any of these findings cannot be made, then this rationale cannot be used to support a conclusion that the claim would have been obvious to one of ordinary skill in the art.

In the instant case, compositions comprising botulinum toxin without complexing proteins are known in the art. See Johnson et al. It is also known in the art that patients develop neutralizing antibodies. See both Carruthers et al and Johnson et al. It is known the art to use botulinum toxin to treat hyperhidrosis. See Heckman et al. Thus, it would be obvious to use a known product in a known method that would do more than yield predictable results. Therefore, absent any convincing evidence to the contrary, the claimed invention is prima facie obvious in view of the combined teachings of Carruthers et al, Heckman et al and Johnson et al.

B. Obvious To Try Rationale

An applicant may argue the examiner is applying an improper "obvious to try" rationale in support of an obviousness rejection.

>An "obvious to try" rationale may support a conclusion that a claim would have been obvious where one skilled in the art is choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success. " [A] person of ordinary skill has good reason to pursue the known options within his or her technical

grasp. If this leads to the anticipated success, it is likely that product [was] not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103." KSR International Co. v. Teleflex Inc., 550 U.S. ___, ___, 82 USPQ2d 1385, 1397 (2007).<

"The admonition that obvious to try' is not the standard under § 103 has been directed mainly at two kinds of error. In some cases, what would have been obvious to try' would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful.... In others, what was obvious to try' was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it." In re O 'Farrell, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988) (citations omitted) (The court held the claimed method would have been obvious over the prior art relied upon because one reference contained a detailed enabling methodology, a suggestion to modify the prior art to produce the claimed invention, and evidence suggesting the modification would be successful.).

In the instant case, it would be obvious to administer pure botulinum toxin to patients that have neutralizing antibodies because Johnson et al teach that the compositions of the invention reduces the chances of patients developing neutralizing

antibodies. There is nothing on the record to show that the combination of prior art references does not teach or suggest the claimed invention.

III. Appellants Specific Arguments Restated

A) Appellant urges that the Examiner has not established a proper case of prima facie obviousness. Appellant urges that the Examiner has not established that all limitations are taught or suggested by the prior art. Appellant urges that Kessler et al and Johnson et al do not teach or suggest the instant claim limitation to administration of a *Clostridium botulinum* neurotoxin which is free of complexing proteins in subjects already exhibiting neutralizing antibodies. Appellant urges that Johnson et al state that “This improvement also reduces the amount of inactive toxin (toxoid) in each vial and thereby lessens the possibility of antibody formation after injection of the preparation into patients”. Appellant urges that the Examiner acknowledges that Johnson et al teach that “ higher specific activity preparations reduce the probability of patients developing neutralizing antibodies". Appellant urges that Johnson et al teach that one way to reduce the number of patients developing neutralizing antibodies would be to develop a more shelf-stable product with a higher specific activity following lyophilization. Appellant urges that Johnson et al teach that a formulation would result in a product that is not antigenic as the currently available product and lesser quantities would be required for treatment". Appellant teaches that Johnson et al state " The toxin is recognized by patient's immune systems as foreign and stimulates antibody production. This renders treatment of the various hyperactive muscle disorders with

botulinum toxin ineffective." Appellant teaches that Johnson et al nor Kessler et al teach the critical claim limitation "wherein the human or animal already exhibits neutralizing antibodies against botulinum neurotoxin complexes". Appellant urges that the Examiner had not established a proper rejection for prima facie obviousness by identifying a motivation to combine the teaching of the prior art references.

B) Appellant urges that the mere fact that references can be combined or modified does not render the resulting combination obvious unless the results would have been predictable to one skilled in the art.

Appellant urges that the Examiner has misapplied and fails to substantiate a finding of obviousness under KSR International Co. v. Teleflex inc. Appellant urges that the improvement method of the cited art according to the Examiner's method has already been demonstrated on the record to be a method which not comparable to the instant method of treating subjects who already exhibits neutralizing antibodies to botulinum toxin complexes. Appellant urges that according to MPEP 2143 interpretation of KSR to reject the claims based on the "obvious to try" exemplary rationale to support a finding of obviousness, the Examiner must articulate a finding that there had been a finite number of identified predictable potential solutions to the recognized need or problem and that one of ordinary skill in the art could have pursued the known potential solutions with a reasonable expectation of success.

III. *Examiner's Response to Applicant's Arguments*

A) In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

In this case, Kessler et al teach long-term treatment of cervical dystonia (CD) with botulinum toxin A (see the Title and the Abstract). Kessler et al teach that the only risk of botulinum toxin injections is the development of serum antibodies against the toxin (see the Abstract).Kessler et al teach that 2% of patients of the study developed neutralizing antibodies (see Abstract). Kessler et al teach that among the 162 patient who discontinued therapy, 17 reported having lost their initially beneficial effect (page 271). Kessler et al teach that at least one of the tests performed detected neutralizing serum antibodies in 9 of the 17 patients who clinically fulfilled the criteria for secondary nonresponse (page 271). Kessler et al teach that secondary nonresponse is one of the major problems in long-term treatment of CD with botulinum toxin A because it entails discontinuing, depriving the patient of the most successful therapy available (page 272). Kessler et al teach that this study confirms that patients at risk of developing neutralizing antibodies are those with high doses administered at relatively short intervals which is in good agreement with previous studies on the issue (page 273).

Kessler et al do not teach the claim limitation "wherein the neurotoxins or mixture of neurotoxins is free of the complexing proteins which naturally form complexes with botulinum neurotoxins and wherein the human or animal already exhibits neutralizing antibodies against botulinum neurotoxin complexes". However, Johnson et al teach compositions of pure botulinum toxin that are free from non-complexing proteins. Johnson et al teach the compositions of the invention reduces the amount of inactive toxin in each vial and thereby lessens the possibility of antibody formation after injection of the composition into patients. One of ordinary skill in the art would reasonably conclude that the compositions taught by Johnson et al comprise botulinum toxin formulations that lessen or reduce neutralizing antibodies because it contains essentially pure botulinum toxin. Johnson et al recognize patients that have developed neutralizing antibodies to the complex are a growing concern in the art, thus this is the very bases for the development of compositions comprising" essentially pure botulinum toxin". Therefore, it would be obvious to administer these compositions to patients that have developed neutralizing antibodies to the botulinum toxin complex. Additionally, *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007), discloses that if a technique has been used to improve one method, and a person of ordinary skill would recognize that it would be used in similar methods in the same way, using the technique is obvious unless its application is beyond that person's skill. *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) also discloses that "The combination of familiar element according to known methods is likely to be obvious when it does no more than yield predictable results". It is well known in the art to use botulinum toxin

complex to treat dystonia or nervous system disorders. See Kessler et al. It is also well known in the art that patients given high dosages of botulinum toxin complex over long periods of time develop neutralizing antibodies. See both Kessler et al and Johnson et al. Johnson et al also recognized that there is a need in the art to solve the problem of the development of neutralizing antibodies to the botulinum toxin complex. Johnson et al provided a solution to this problem, by preparing a product that is a pure neurotoxin instead of the complex. Thus, it would be obvious to administer an essential pure composition of botulinum toxin (e.g. free of complexing proteins) to patients that have neutralizing antibodies because the composition of essentially pure botulinum toxin was developed to lessen or reduce the amount of neutralizing antibodies produced in patients after administration of the composition. It should also be noted that "obvious to try" is proper when there is a finding of a recognized problem or need in the art including a design need or market pressure to solve a problem, a finding that there has been a finite number of identified predictable potential solutions and a finding that one of ordinary skill in the art could have pursed the known potential options with a reasonable expectation of success. See KSR International Co. v. Teleflex Inc., 220 U.S. -, 82 USPQ2d 1385 (2007).

In the instant case, there is a need in the art to find a solution to the problem of development of neutralizing antibodies in patients administered botulinum toxin complex over long periods of time. Since these patients exist there is the problem of treating these patients after botulinum toxin complex injection has failed. Johnson et al developed compositions of essentially pure botulinum toxin to overcome these problems

recognized in the prior art. This provides further support as to why one of skill in the art would administer a composition of essentially pure botulinum toxin to patients that have developed neutralizing antibodies to botulinum toxin complex.

In response to Applicant's comments regarding, Johnson et al, as stated above, it is the Examiner's position that Applicant has mischaracterized this passage in Johnson et al. It should be noted that the passage in question is in the Background Section of Johnson et al. In this passage, Johnson et al explain problems in the art associated with patients that have developed neutralizing antibodies to the botulinum toxin complex. Johnson et al recognized the problems associated with patients that have developed neutralizing antibodies to the complex and thus, developed compositions of "essentially pure botulinum toxin" which reduces the amount of inactive toxin in each vial and thereby lessens the possibility of antibody formation after injection of the composition into patients. Therefore, Johnson et al do not teach away from the claimed invention, but in fact, solve the problem associated with patients that have developed neutralizing antibodies to botulinum toxin complex. Therefore, administration of the pure botulinum toxin as taught by Johnson et al to patients that have developed neutralizing antibodies as recognized by the art would be effective.

To address Appellant's argument regarding, Johnson et al statement regarding treatment of the various hyperactive muscle disorders with botulinum toxin ineffective, it should be noted that Johnson et al teach that one of the major drawbacks to the use of botulinum toxin is development of antibodies or other types of immunity by patients (column 1). Johnson et al states:

> "The toxin is recognized by the patient's immune systems as foreign and stimulates antibody production. *Johnson et al teach that this renders treatment of various hyperactive muscle disorders with botulinum toxin ineffective.* One way to reduce the number of patients developing neutralizing antibodies would be to develop neutralizing antibodies would be to develop a more shelf-stable product with a higher specific activity following lyophilization. Such a formulation would result in a product that is not antigenic as the currently available product and lesser quantities of toxin would be required for treatment" (column 1).

The context of this passage discloses that the art recognizes that there is a population of patients that have developed neutralizing antibodies. This passage also suggest that a way to reduce the development of neutralizing antibodies is to produce a product with a higher specific activity. Johnson et al has developed such a product, e.g. purified botulinum toxin (without complexing proteins). The statement regarding "Johnson et al teach that this renders treatment of various hyperactive muscle disorders with botulinum toxin ineffective" refers to the *previous products* of the art, e.g. botulinum toxin complex (containing neutralizing antibodies)(e.g. BOTOX®) which includes complexing proteins. This statement does not refer to the ineffectiveness of the products taught by Johnson et al.

To address Appellant's arguments regarding KSR, it should be remembered that MPEP section 2145 states:

> ">A suggestion or motivation to combine references is an appropriate method for determining obviousness, however it is just one of a number of valid rationales for doing so. The Court in KSR identified several exemplary rationales to support a conclusion of obviousness which are consistent with the proper "functional approach" to the determination of obviousness as laid down in

Graham. KSR, 550 U.S. at ___, 82USPQ2d at 1395-97. See MPEP § 2141 and § 2143.<

The claimed invention falls within at least two areas of exemplary rationales available under KSR, 550 U.S. at ___, 82USPQ2d at 1395-97. The rationales are as follows:

A. Combining Prior Art Elements According to Known Methods To Yield Predictable Results

The rationale to support a conclusion that the claim would have been obvious is that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination yielded nothing more than predictable results to one of ordinary skill in the art. KSR, 550 U.S. at ___, 82 USPQ2d at 1395; Sakraida v. AG Pro, Inc., 425 U.S. 273, 282, 189 USPQ 449, 453 (1976); Anderson 's-Black Rock, Inc. v. Pavement Salvage Co., 396 U.S. 57, 62-63, 163 USPQ 673, 675 (1969); Great Atlantic & P. Tea Co. v. Supermarket Equipment Corp., 340 U.S. 147, 152, 87 USPQ 303, 306 (1950). "[I]t can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." KSR, 550 U.S. at ___, 82 USPQ2d at 1396. If any of these findings cannot be made, then this rationale cannot be used to support a conclusion that the claim would have been obvious to one of ordinary skill in the art.

In the instant case, compositions comprising botulinum toxin without complexing proteins are known in the art. See Johnson et al. It is also known in the art that patients develop neutralizing antibodies. See both Kessler et al and Johnson et al. It is

known in the art to use botulinum toxin to treat cervical dystonia with botulinum toxin. See Kessler et al. Thus, it would be obvious to use a known product in a known method that would do more than yield predictable results.

B. Obvious To Try Rationale

An applicant may argue the examiner is applying an improper "obvious to try" rationale in support of an obviousness rejection.

>An "obvious to try" rationale may support a conclusion that a claim would have been obvious where one skilled in the art is choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success. " [A] person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely that product [was] not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103." KSR International Co. v. Teleflex Inc., 550 U.S. ___, ___, 82 USPQ2d 1385, 1397 (2007).<

"The admonition that obvious to try' is not the standard under § 103 has been directed mainly at two kinds of error. In some cases, what would have been obvious to try' would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful.... In others, what was obvious to try' was to explore a new

technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it." In re O 'Farrell, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988) (citations omitted) (The court held the claimed method would have been obvious over the prior art relied upon because one reference contained a detailed enabling methodology, a suggestion to modify the prior art to produce the claimed invention, and evidence suggesting the modification would be successful.).

In the instant case, it would be obvious to administer pure botulinum toxin to patients that have neutralizing antibodies because Johnson et al teach that the compositions of the invention reduces the chances of patients developing neutralizing antibodies. There is nothing on the record to show that the combination of prior art reference does not teach or suggest the claimed invention.

IV. Appellants Specific Arguments Restated

A) Appellant urges that the Examiner has not established a proper case of prima facie obviousness. Appellant urges that the Examiner has not established that all limitations are taught or suggested by the prior art. Appellant urges that Goschel et al and Johnson et al do not teach or suggest the instant claim limitation to administration of a *Clostridium botulinum* neurotoxin which is free of complexing proteins in subjects already exhibiting neutralizing antibodies. Appellant urges that Johnson et al state that "This improvement also reduces the amount of inactive toxin (toxoid) in each vial and thereby lessens the possibility of antibody formation after injection of the

preparation into patients". Appellant urges that the Examiner acknowledges that Johnson et al teach that " higher specific activity preparations reduce the probability of patients developing neutralizing antibodies". Appellant urges that Johnson et al teach that one way to reduce the number of patients developing neutralizing antibodies would be to develop a more shelf-stable product with a higher specific activity following lyophilization. Appellant urges that Johnson et al teach that a formulation would result in a product that is not antigenic as the currently available product and lesser quantities would be required for treatment". Appellant teaches that Johnson et al state " The toxin is recognized by patient's immune systems as foreign and stimulates antibody production. This renders treatment of the various hyperactive muscle disorders with botulinum toxin ineffective." Appellant teaches that Johnson et al nor Goschel et al teach the critical claim limitation "wherein the human or animal already exhibits neutralizing antibodies against botulinum neurotoxin complexes". Appellant urges that the Examiner had not established a proper rejection for prima facie obviousness by identifying a motivation to combine the teaching of the prior art references.

B) Appellant urges that the mere fact that references can be combined or modified does not render the resulting combination obvious unless the results would have been predictable to one skilled in the art.

Appellant urges that the Examiner has misapplied and fails to substantiate a finding of obviousness under KSR International Co. v. Teleflex inc. Appellant urges that the improvement method of the cited art according to the Examiner's method has

already been demonstrated on the record to be a method which not comparable to the instant method of treating subjects who already exhibits neutralizing antibodies to botulinum toxin complexes. Appellant urges that according to MPEP 2143 interpretation of KSR to reject the claims based on the "obvious to try" exemplary rationale to support a finding of obviousness, the Examiner must articulate a finding that there had been a finite number of identified predictable potential solutions to the recognized need or problem and that one of ordinary skill in the art could have pursued the known potential solutions with a reasonable expectation of success.

IV. *Examiner's Response to Applicant's Arguments*

A) In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

In this case, Goschel et al teach a method of using botulinum toxin to treat patients having torticollis spasmodicus, facial dystonias, torsion dystonia and spasticity patients (pages 98-99 and Table 3, page 101). Goschel et al also teach patients that have developed neutralizing antibodies against botulinum toxin A complex (pages 98-99 and Table 3, page 101). Goschel et al teach that neutralizing antibodies were the cause

of therapeutic failure (page 101). Goschel et al teach that based on theses studies, second generation botulinum neurotoxin preparations should be devoid of toxoid and should be purified from concomitant proteins, this will reduce the load of foreign substances that might lead to untoward reactions (page 102). Goschel et al do not teach the claim limitation "wherein the neurotoxins or mixture of neurotoxins is free of the complexing proteins which naturally form complexes with botulinum neurotoxins and wherein the human or animal already exhibits neutralizing antibodies against botulinum neurotoxin complexes". However, Johnson et al teach compositions of pure botulinum toxin that are free from non-complexing proteins. Johnson et al teach the compositions of the invention reduces the amount of inactive toxin in each vial and thereby lessens the possibility of antibody formation after injection of the composition into patients. One of ordinary skill in the art would reasonably conclude that the compositions taught by Johnson et al comprise botulinum toxin formulations that lessen or reduce neutralizing antibodies because it contains essentially pure botulinum toxin. Johnson et al recognize patients that have developed neutralizing antibodies to the complex are a growing concern in the art, thus this is the very bases for the development of compositions comprising" essentially pure botulinum toxin". Therefore, it would be obvious to administer these compositions to patients that have developed neutralizing antibodies to the botulinum toxin complex. Additionally, *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007), discloses that if a technique has been used to improve one method, and a person of ordinary skill would recognize that it would be used in similar methods in the same way, using the technique is obvious unless its

application is beyond that person's skill. *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) also discloses that "The combination of familiar element according to known methods is likely to be obvious when it does no more than yield predictable results". It is well known in the art to use botulinum toxin complex to treat dystonia or nervous system disorders. See Goschel et al. It is also well known in the art that patients given high dosages of botulinum toxin complex over long periods of time develop neutralizing antibodies. See both Goschel et al and Johnson et al. Johnson et al also recognized that there is a need in the art to solve the problem of the development of neutralizing antibodies to the botulinum toxin complex. Johnson et al provided a solution to this problem, by preparing a product that is a pure neurotoxin instead of the complex. Thus, it would be obvious to administer an essential pure composition of botulinum toxin (e.g. free of complexing proteins) to patients that have neutralizing antibodies because the composition of essentially pure botulinum toxin was developed to lessen or reduce the amount of neutralizing antibodies produced in patients after administration of the composition. It should also be noted that "obvious to try" is proper when there is a finding of a recognized problem or need in the art including a design need or market pressure to solve a problem, a finding that there has been a finite number of identified predictable potential solutions and a finding that one of ordinary skill in the art could have pursed the known potential options with a reasonable expectation of success. See KSR International Co. v. Teleflex Inc., 220 U.S. -, 82 USPQ2d 1385 (2007).

In the instant case, there is a need in the art to find a solution to the problem of development of neutralizing antibodies in patients administered botulinum toxin complex over long periods of time. Since these patients exist there is the problem of treating these patients after botulinum toxin complex injection has failed. Johnson et al developed compositions of essentially pure botulinum toxin to overcome these problems recognized in the prior art. This provides further support as to why one of skill in the art would administer a composition of essentially pure botulinum toxin to patients that have developed neutralizing antibodies to botulinum toxin complex.

In response to Applicant's comments regarding, Johnson et al, as stated above, it is the Examiner's position that Applicant has mischaracterized this passage in Johnson et al. It should be noted that the passage in question is in the Background Section of Johnson et al. In this passage, Johnson et al explain problems in the art associated with patients that have developed neutralizing antibodies to the botulinum toxin complex. Johnson et al recognized the problems associated with patients that have developed neutralizing antibodies to the complex and thus, developed compositions of "essentially pure botulinum toxin" which reduces the amount of inactive toxin in each vial and thereby lessens the possibility of antibody formation after injection of the composition into patients. Therefore, Johnson et al do not teach away from the claimed invention, but in fact, solve the problem associated with patients that have developed neutralizing antibodies to botulinum toxin complex. Therefore, administration of the pure botulinum toxin as taught by Johnson et al to patients that have developed neutralizing antibodies as recognized by the art would be effective.

To address Appellant's argument regarding, Johnson et al statement regarding treatment of the various hyperactive muscle disorders with botulinum toxin ineffective, it should be noted that Johnson et al teach that one of the major drawbacks to the use of botulinum toxin is development of antibodies or other types of immunity by patients (column 1). Johnson et al states:

> "The toxin is recognized by the patient's immune systems as foreign and stimulates antibody production. *Johnson et al teach that this renders treatment of various hyperactive muscle disorders with botulinum toxin ineffective.* One way to reduce the number of patients developing neutralizing antibodies would be to develop neutralizing antibodies would be to develop a more shelf-stable product with a higher specific activity following lyophilization. Such a formulation would result in a product that is not antigenic as the currently available product and lesser quantities of toxin would be required for treatment" (column 1).

The context of this passage discloses that the art recognizes that there is a population of patients that have developed neutralizing antibodies. This passage also suggest that a way to reduce the development of neutralizing antibodies is to produce a product with a higher specific activity. Johnson et al has developed such a product, e.g. purified botulinum toxin (without complexing proteins). The statement regarding "Johnson et al teach that this renders treatment of various hyperactive muscle disorders with botulinum toxin ineffective" refers to the *previous products* of the art, e.g. botulinum toxin complex (containing neutralizing antibodies)(e.g. BOTOX®) which includes complexing proteins. This statement does not refer to the ineffectiveness of the products taught by Johnson et al.

To address Appellant's arguments regarding KSR, it should be remembered that MPEP section 2145 states:

> ">A suggestion or motivation to combine references is an appropriate method for determining obviousness, however it is just one of a number of valid rationales for doing so. The Court in KSR identified several exemplary rationales to support a conclusion of obviousness which are consistent with the proper "functional approach" to the determination of obviousness as laid down in Graham. KSR, 550 U.S. at ___, 82USPQ2d at 1395-97. See MPEP § 2141 and § 2143.<

The claimed invention falls within at least two areas of exemplary rationales available under KSR, 550 U.S. at ___, 82USPQ2d at 1395-97. The rationales are as follows:

A. Combining Prior Art Elements According to Known Methods To Yield Predictable Results

The rationale to support a conclusion that the claim would have been obvious is that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination yielded nothing more than predictable results to one of ordinary skill in the art. KSR, 550 U.S. at ___, 82 USPQ2d at 1395; Sakraida v. AG Pro, Inc., 425 U.S. 273, 282, 189 USPQ 449, 453 (1976); Anderson 's-Black Rock, Inc. v. Pavement Salvage Co., 396 U.S. 57, 62-63, 163 USPQ 673, 675 (1969); Great Atlantic & P. Tea Co. v. Supermarket Equipment Corp., 340 U.S. 147, 152, 87 USPQ 303, 306 (1950). "[I]t can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." KSR, 550 U.S. at ___, 82 USPQ2d at 1396. If any of these findings cannot be made, then this rationale cannot be used to support a

conclusion that the claim would have been obvious to one of ordinary skill in the art.

In the instant case, compositions comprising botulinum toxin without complexing proteins are known in the art. See Johnson et al. It is also known in the art that patients develop neutralizing antibodies. See both Goschel et al and Johnson et al. It is known to use botulinum toxin to treat torticollis spasmodicus, facial dystonias, torsion dystonia and spasticity patients. See Goschel et al. Thus, it would be obvious to use a known product in a known method that would do more than yield predictable results.

B. Obvious To Try Rationale

An applicant may argue the examiner is applying an improper "obvious to try" rationale in support of an obviousness rejection.

>An "obvious to try" rationale may support a conclusion that a claim would have been obvious where one skilled in the art is choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success. " [A] person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely that product [was] not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103." KSR International Co. v. Teleflex Inc., 550 U.S. ___, ___, 82 USPQ2d 1385, 1397 (2007).<

"The admonition that obvious to try' is not the standard under § 103 has been directed mainly at two kinds of error. In some cases, what would have been obvious to try' would

have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful.... In others, what was obvious to try' was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it." In re O 'Farrell, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988) (citations omitted) (The court held the claimed method would have been obvious over the prior art relied upon because one reference contained a detailed enabling methodology, a suggestion to modify the prior art to produce the claimed invention, and evidence suggesting the modification would be successful.).

In the instant case, it would be obvious to administer pure botulinum toxin to patients that have neutralizing antibodies because Johnson et al teach that the compositions of the invention reduces the chances of patients developing neutralizing antibodies. There is nothing on the record to show that the combination of prior art reference does not teach or suggest the claimed invention.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the Examiner should be affirmed.

Respectfully submitted,

/Vanessa L. Ford/

Examiner, Art Unit 1645

December 31, 2008

Conferees:

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